REMARKS

By this amendment, Applicants have amended the specification to remove the hyperlink as recommended by the Examiner. Applicants have also amended claim 1 to include that the mobility reducing moiety includes a polynucleotide segment and that after primer extension is performed, breakdown products and residual labeled nucleotide terminators in the mixture are not washed away. Support for the amendments to claim 1 can be found in the specification, for example, at page 19, line 30 to page 20, line 5, page 28, lines 3-6 and claim 11. Claim 10 has been amended to remove the term "substantially" and claim 11 has been canceled without disclaimer. These amendments do not add new matter. Applicants respectfully request entry of these amendments and allowance of the pending claims.

Rejections Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 10 and 11 as allegedly indefinite. The Examiner considers the phrase "substantially bind" in claims 10 and 11 as allegedly indefinite. Applicants respectfully disagree with the Examiner. However, solely to expedite prosecution and without acquiescing to the Examiner's rejection, Applicants have removed the term "substantially" from claim 10 and canceled claim 11. Thus, this rejection is now moot and Applicants request reconsideration and withdrawal of this rejection based on 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 1-3, 15 and 16 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,484,701 (Cocuzza). The Examiner also rejected claims 1-5, and 7-16 under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Publication No. 2005/0112608 (Grossman '608). Applicants respectfully traverse these rejections.

To establish a *prima facie* case of anticipation under 35 U.S.C. §102 each and every element of the claims must be disclosed in the cited prior art reference. The

present claims include, among other things, that the mobility-reducing moiety contains a polynucleotide segment and that breakdown products and residual labeled nucleotide terminators in the mixture are not washed away before electrophoresis is performed. Neither Cocuzza nor Grossman disclose these features.

Cocuzza discloses conducting primer extension using a biotin labeled primer and immobilizing the biotin labeled primer on a biotin-binding protein attached to a solid support and treating any bound biotin labeled primer with a denaturant to dissociate bound primer extension products, then separating the mixture to detect biotin labeled extended primer. (Cocuzza Summary of Invention, col. 4, lines 1-15). Cocuzza does not disclose in any way that the primers contain a polynucleotide segment as a mobility-reducing moiety or any way to avoid time consuming washing steps before electrophoresis as currently claimed.

As to Grossman '608, this reference discloses DNA sequencing using a polymer chain attached to a polynucleotide, where the polymer chain imparts a distinctive ratio of charge/translational frictional drag. The polymers described in Grossman '608 are non-polynucleotide polymers, such as for example, polyethylene oxide, polypeptides, polyamidoamine branched polymers, or the like. (Grossman at ¶95-97). Grossman '608 describes polynucleotides as highly charged molecules that require an uncharged polymer chain for sequencing.

> Where the binding polymers are highly charged, as in the case of oligonucleotides, **the polymer chains are preferably uncharged**. (Grossman '608 ¶95, emphasis added)

Following the disclosure of Grossman '608, one of ordinary skill in the art would use an uncharged polymer chain (not a polynucleotide) attached to a primer when sequencing DNA.

In contrast to Grossman '608, the currently amended claims include that the mobility-reducing moiety comprises a polynucleotide segment (a charged polymer) that is attached to a polynucleotide primer (another charged polymer), both of which are

employed in the sieving matrix. See, for example, the specification page 19, line 30 to page 20, line 9.

The Examiner alleges that Grossman '608 "teaches polynucleotide mobility modifiers of at least 20 additional nucleotides" and points to Grossman '608 ¶119-120. (Office Action at page 8). However, on a fair and accurate reading of paragraphs 119 and 120, the mobility modifier described in Grossman '608 is not a polynucleotide at all but a non-polynucleotide polymer chain (e.g., PEO), which is built up on the target binding oligonucleotide.

> Coupling of the **polymer chains to an oligonucleotide** can be carried out by an extension of conventional phosphoramidite oligonucleotide synthesis methods, or by other standard coupling methods. FIG. 4A illustrates a procedure for coupling **a PEO polymer chain to the 5' end of an oligonucleotide** formed on a solid support, via phosphoramidite coupling. FIG. 4B illustrates the coupling of the above bisurethane tolyl-linked polymer chain to an oligonucleotide on a solid support, also via phosphoramidite coupling. Details of the two coupling methods are given in Examples 3B and 3C, respectively.
>
> Alternatively, the **polymer chain can be built up on an oligonucleotide (or other sequence-specific binding polymer)** by stepwise addition of polymer-chain units to the oligonucleotide, using standard solid-phase synthesis methods. (Grossman '608 ¶119 and 120, emphasis added)

Thus, Grossman '608 discloses that the oligonucleotide (polynucleotide) binds the target sequence and not that the oligonucleotide (polynucleotide) is the mobility reducing moiety that does not bind the target. Moreover, Grossman '608 says nothing about avoiding one or more wash steps to remove terminator breakdown products and residual labeled nucleotide terminators before electrophoresis. In fact, Grossman '608 does not mention terminator breakdown products and residual labeled nucleotide terminators at all.

In summary, neither Cocuzza nor Grossman '608 disclose, among other things, that the mobility-reducing moiety contains a polynucleotide segment or ways to avoid

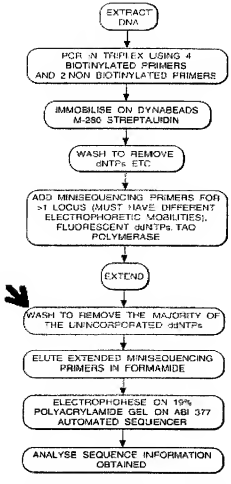
one or more wash steps before electrophoresis. Accordingly, Cocuzza and Grossman '608 do not anticipate the claims and Applicants request that the rejections under 35 U.S.C. §102 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-6 and 7-16 under 35 U.S.C. §103(a) for allegedly being obvious over WO 96/06187A1 (Tully) in view of Cocuzza or Tully in view of Cocuzza and U.S. Patent No. 5,656,145 (Nguyen). The Examiner also rejects claims 6 and 12-14 as allegedly being obvious over Grossman '608 alone or in view of Nguyen. Applicants respectfully traverse these rejections.

A prior art reference cannot render an invention obvious if the reference teaches away from the claimed invention. *KSR International Co. v. Teleflex Inc.* 127 S. Ct. 1727, 1734. Tully teaches immobilizing the target sequence and conducting sequencing using minisequencing primers. After the minisequencing primers are extended using ddNTPs, unincorporated ddNTPs are washed away. Figure 2 of Tully teaches the steps in his sequencing methods.

Fig.2.



Thus, Tully teaches washing the labeled terminator nucleotides away before electrophoresis. In contrast, the present claims include, among other things, that breakdown products and residual labeled nucleotide terminators in the mixture are not washed away before electrophoresis is performed. Tully specifically teaches away from this feature.

The teachings of more than one reference may be considered in combination provided one of ordinary skill in the art would combine the references in that way to solve the problem facing the inventor. *KSR International Co. v. Teleflex Inc.* 127 S. Ct. 1727, 1733. With regard to Cocuzza, as stated above, Cocuzza does not disclose in any way that the primers contain a polynucleotide segment as a mobility-reducing moiety or any way to avoid one or more washing steps before electrophoresis as currently claimed.

One of ordinary skill in the art would not combine Tully with Cocuzza because they do not solve the problem caused by interfering signals from detectable breakdown products and residual labeled terminator nucleotides and the problems of time consuming washing steps.

Nguyen discloses a needle guide that helps the user load a sample into a slab gel (col. 1., lines 28-30). Nguyen does not disclose in any way primers that contain a polynucleotide segment as a mobility-reducing moiety or any way to avoid time consuming washing steps before electrophoresis as currently claimed. One of ordinary skill in the art would not combine Nguyen with Tully and Cocuzza because they do not solve the problem caused by interfering signals from detectable breakdown products and residual labeled terminator nucleotides and the problems of time consuming washing steps.

With regard to Grossman '608, as stated above, the polymers described in Grossman '608 are non-polynucleotide polymers, such as for example, polyethylene oxide, polypeptides, polyamidoamine branched polymers, or the like. (Grossman at ¶95-97). Grossman '608 describes polynucleotides as highly charged molecules that require an uncharged polymer chain for sequencing.

> Where the binding polymers are highly charged, as in the case of oligonucleotides, **the polymer chains are preferably uncharged**. (Grossman '608 ¶95, emphasis added)

Following the teachings of Grossman '608, one of ordinary skill in the art would use an uncharged polymer chain (not a polynucleotide) attached to a primer when sequencing DNA.

In contrast to Grossman '608, the currently amended claims include that the mobility-reducing moiety comprises a polynucleotide segment (a charged polymer) that is attached to a polynucleotide primer (another charged polymer).

Moreover, Grossman '608 says nothing about avoiding one or more wash steps to remove terminator breakdown products and residual labeled nucleotide terminators

before electrophoresis. In fact, Grossman '608 does not mention terminator breakdown products and residual labeled nucleotide terminators at all.

As stated above, Nguyen does not disclose in any way primers that contain a polynucleotide segment as a mobility-reducing moiety or any way to avoid time consuming washing steps before electrophoresis as currently claimed. One of ordinary skill in the art would not combine Nguyen with Grossman '608 because they do not solve the problem caused by interfering signals from detectable breakdown products and residual labeled terminator nucleotides and the problems of time consuming washing steps.

Applicants respectfully submit the claims cannot be considered obvious over any of the cited references alone or in combination. Accordingly, Applicants request that the rejections under 35 U.S.C. §103(a) be reconsidered and withdrawn.

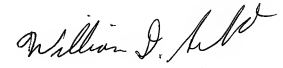
Conclusion

Reconsideration and allowance are respectfully solicited.

Applicants petition the Commissioner for a 2-month extension of time. No additional fee is believed to be due with respect to the filing of this amendment. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided.

Respectfully submitted,



William D. Schmidt
Registration No.: 39,492
Attorney for Applicants

Kalow & Springut LLP
Telephone No.: (212) 813-1600